147. (Amended) The isolated polynucleotide molecule of claim 133, wherein said modification within the genome or antigenome comprising a partial or complete gene deletion[, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene] specifies a change in phenotype for the resultant recombinant virus selected from: a change in growth characteristics in culture, small plaque size, attenuation in vivo, temperature-sensitivity, cold-adaptation, host range restriction, change in antigen expression, or a change in immunogenicity.

Please cancel claims 79-87, 123-127, 146, 162, and 163, without prejudice.

REMARKS

With Entry of this Amendment, claims 63-78, 88-122, 128-145, and 147-161 are pending in the application. By this Amendment, claims 63, 70, 71, 73, 74, 88, 122, 129, 132, 133, 139, 140, 141, and 147 have been amended and claims 79-87, 123-127, 146, 162, and 163 canceled (withdrawn from consideration), without prejudice.

Subject matter presented within the claims as amended is believed to correspond generically to group I set forth in the Restriction Requirement, which is hereby elected with traverse by way of presentation of the amended claims herein.

The present Amendment is intended to resolve restriction practice issues in this application following the course of informal telephone interviews conducted with Examiner Brumback on October 2, 2000 and November 7, 2000. The focus of these interviews was to request clarification and reconsideration of the Restriction Requirement by the Examiner, to determine an efficient, consistent process for examining the subject matter of the application in a manner that does not present an undue burden on either the Office or Applicants.

It was noted during these interviews that two Restriction Requirements, pending in this case and in a related (Serial No. 09/291,894) ('894) application based on a common parent application Serial No. 08/892,403 ('403) (now issued as U.S. Patent No. 5,993,824 ('824)), proscribe a total of 33 separate groups initially proposed to constitute separate and distinct inventions. It was further noted that a Restriction Requirement in the parent, '403

application set forth only 9 groups proposed as distinct inventions. One of these groups (recombinant RSV incorporating temperature sensitive mutations) was elected and prosecuted to become the issued '824 patent. Another group specified in the parental Restriction Requirement, group II (relating to gene deletion/ablation mutants) was generally selected as the foundational subject matter of claims in the present application. Yet another application is on file with the Office (Serial No. 09/444,221) presenting claims directed to additional subject matter restricted in the parent case (RSV with modification to a cis-acting regulatory sequence such as a promoter, GS or GE signal sequence). All three of these applications are commonly assigned to Examiner Brumback for review.

Applicants requested during the above-noted interviews that the proposed restrictions in the present application, as well as in the related applications pending before Examiner Brumback, be reconsidered in an effort to avert the high costs, inefficiency, and potentially inconsistent examination that might attend separate prosecution of the various restricted groups. In this regard, Applicants' representative submitted that many of the restricted groups relate to species that can be examined together. In particular, it was suggested that certain dependent and "combinatorial" aspects of the invention are sufficiently related that they would not create an undue burden on the Office to examine them coordinately. Notably, many of these dependent and combinatorial aspects within the generic invention are independently claimed in related applications which are, or may prospectively be, assigned to Examiner Brumback—hopefully minimizing any additional searching and examination burdens that might otherwise attend their coordinate prosecution.

During the course of the above-referenced interviews, Examiner Brumback made numerous helpful suggestions which clarified the course of restriction practice in the application. The present Amendment is now filed in reply to these suggestions, hoping to follow faithfully the proposals made by the Examiner to advance the case to substantive prosecution.

As an initial point, Examiner Brumback courteously specified during the November 7, 2000 interview that it would not be fruitful to maintain co-prosecution of claims

directed to recombinant RSV compositions alongside claims to methods for producing recombinant RSVs, and methods for stimulating an immune response involving administration of the recombinant viruses. In response, Applicants have canceled or amended the claims herein for clarity to withdraw, without prejudice, claims directed to methods for stimulating an immune response (claims 123-127) and to methods for producing recombinant RSVs (claims 162 and 163). Applicants reserve the right to file one or more divisional or other related application(s) to this non-elected subject matter.

Examiner Brumback also kindly indicated that it would not impose and undue burden on the Office to examine together certain closely related subject matter, as exemplified by the following groups: recombinant, chimeric viruses; isolated polynucleotides encoding the recombinant, chimeric viral genome; vectors incorporating these polynucleotides; and host cells transfected or transformed by the foregoing vectors. Thus, the claims as amended herein embrace these related aspects of the invention for coordinate prosecution. Following this direction by the Examiner, Applicants' representative submitted during the November 7, 2000 interview that claims to immunogenic compositions (e.g., vaccines) containing the foregoing recombinant viruses might also be prosecuted coordinately with the foregoing groups without undue burden. Such claims therefore remain in the application for the Examiner's consideration. It is noted in this context that the issued '824 patent from the '403 parent application includes claims that span a similar range of related subject matter.

Another important issue which was not resolved during the Interview relates to the grouping of claims for recombinant RSVs having a "change in gene position", which may result from a gene deletion or other changes (e.g., rearrangement, insertion, etc.) To facilitate prosecution of the application, Applicants have withdrawn this subject matter from consideration by amending the independent claims and by cancellation of certain specific claims (e.g., claims 79-87, and 146). Applicants reserve the right to file one or more divisional or other related application(s) to this non-elected subject matter

A slightly more complex issue which was not resolved during the Interview relates to the grouping of claims directed to RSV having a gene "deletion" and/or having a

gene "knock-out" that modulates gene expression without actual removal of all or part of a gene coding sequence. Applicants originally presented this subject matter in the form of a Markush group (see, e.g., original claim 63), because of the close functional relationship between RSV deletion mutants and RSV having a gene knock-out by, e.g., introduction of a stop codon or alteration of a start codon that ablates or reduces gene expression. Applicants respectfully request that this subject matter be considered together. However, the claim have been amended herein to segregate gene deletion and knock-out mutants, with the latter restricted group now relegated to claims 70-78 and 139-145. If the Examiner declines to reconsider the restriction of these claims from the elected claims directed to RSV gene deletion mutants and related subject matter, they can be readily withdrawn from consideration without further amendment.

With regard to claims which present dependent or "combinatorial" aspects of the invention, the Examiner stated a general agreement that these aspects of the invention could be viewed as "species" within a defined genus. For example, a genus defined as RSV having a gene deletion may incorporate a partial or complete gene deletion of one or more different gene(s) or genome segment(s) from the NS1, NS2, N, P, M, SH, M2(ORF1), M2(ORF2), L, F or G genes. However, the invention further contemplates important "combinatorial" modifications for vaccine development, which cannot be efficiently dissected away from Applicant's generic invention defined, e.g., by a recombinant human RSV having a gene deletion.

In this regard, Applicants' invention depends in specific embodiments on the use of a combination of modifications selected from a diverse "menu" of useful genetic manipulations—to provide an optimal, live-attenuated vaccine candidate for a selected population of target vacinees (e.g., seronegative versus seropositive infants). In this context, it will often be desired, for example, to combine the basic RSV deletion mutant construction with one or more attenuating mutations, or other nucleotide changes, that specify a desired phenotype. For example, Applicants have clearly shown how to introduce temperature-sensitive and other types of attenuating point mutations in combination with gene deletions and other changes (e.g., these changes incorporated within a chimeric human-human or human-

bovine RSV). These and other combinatorial-designed viruses are fully supported by the disclosure and Examples of the specification. Further, these dependent aspects are believed sufficiently related that their common examination would not impose an undue burden on the Office. In particular, searching and review of published materials relating to RSV having gene deletions is expected to largely comprehend the art relating to species of RSV having such deletions along with additional modifications, as presently claimed. This is particularly true if separate applications directed independently to these aspects, only claimed in the present application as dependent, "combinatorial" aspects within a defined genus, are before the Examiner simultaneously.

For the foregoing reasons, Applicants respectfully submit that the claims presented herein are consistent with the provisions and policies governing restriction practice in the PTO, particularly with regard to coordinate presentation and examination of genus/species claims. Collective examination of these claims is therefore earnestly solicited.

The Examiner is kindly invited to telephone the undersigned at 206-467-9600 if further discussion of the foregoing restriction practice issues is desired.]

Respectfully submitted,

Dated: 11/29/00

Jeffrey J. King
Reg. No. 38,515

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (206) 467-9600
Fax: (415) 576-0300
JJK:lmp

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